1644

PATENT

Attorney Docket No. **UM-04594**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Peter A. Ward *et al.*		
Serial No.:	09/651,685	Group No.:	1644
Filed:	08/30/00	Examiner:	Decloux, A
Entitled:	**Compositions And Methods For The Treatment Of Sepsis**		

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: March 24, 2003 By: _____
Christopher J. Collins

Sir or Madam:

Enclosed please find an Information Disclosure Statement and Form PTO-1449, including copies of the references contained thereon, for filing in the U.S. Patent and Trademark Office.

A check for $180.00 is also enclosed pursuant to 37 C.F.R. § 1.17(p) for filing this Information Disclosure Statement after three months as set forth in 37 C.F.R. § 1.97(c).

The Commissioner is hereby authorized to charge any additional fee or credit overpayment to our Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: March 24, 2003

_____
Peter G. Carroll
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Dated: March 24, 2003 By: Christopher J. Collins

Sir or Madam:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are referred to in the body of the specification:

- U.S. Pat. 4,357,272 to Polson;
- U.S. Pat. 5,051,448 to Shashoua;
- U.S. Pat. 5,169,862 to Burke, Jr., *et al.*;
- U.S. Pat. 5,192,746 to Lobl, *et al.*;
- U.S. Pat. 5,260,203 to Ladner *et al.*;
- U.S. Pat. 5,539,085 to Bischoff, *et al.*;
- U.S. Pat. 5,559,103 to Gaeta *et al.*;
- U.S. Pat. 5,565,332 to Hoogenboom *et al.*;
- U.S. Pat. 5,576,423 to Aversa *et al.*;

- U.S. Pat. 5,585,089 to Queen *et al*;
- U.S. Pat. 5,658,727 to Barbas *et al.*;
- U.S. Pat. 5,904,922 to Carroll;
- EP 0025949 to Kramer *et al.*;
- G.W. Machiedo *et al.*,"Patterns of Mortality in a Surgical Intensive Care Unit," *Surg. Gyn. & Obstet.* 152:757-759 (1981);
- D.D. Morris *et al.*,"Endotoxemia in neonatal calves given antiserum to a mutant *Escherichia coli* (J-5)," *Am. J. Vet. Res.* 47:2554-2565 (1986);
- A.M. Hoffman *et al.*,"Prognostic Variables for Survival of Neonatal Foals Under Intensive Care," *J. Vet. Int. Med.* 6:89-95 (1992);
- S.M. Wolff,"Monoclonal Antibodies and the Treatment of Gram-Negative Bacteremia and Shock," *New Eng. J. Med.* 324:486-488 (1991);
- K.A. Schulman *et al.*,"Cost-effectiveness of HA-1A Monoclonal Antibody for Gram-Negative Sepsis," *JAMA* 266:3466-3471 (1991);
- Mandecki W, *et al.*,"Chemical synthesis of a gene encoding the human complement fragment C5a and its expression in *Escherichia coli*," *Proc Natl Acad Sci* U S A. 82(11):3543-7 (1985);
- Kohl, J.,and Bitter-Suermann, D., *Anaphylatoxins. Complement in health and disease.*, Edited by Whaley, K., Loos, M., Weiler, J.M., Kluwer Academic publishers, pp 299-324 (1993);
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- Van Epps, *et al.*,"Relationship of C5a Receptor Modulation to the Functional Responsiveness of Human Polymorphonuclear Leukocytes to C5a," *J. Immunol.* 150:246-252 (1993);
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- Kohler, G. and Milstein, C., "Continous cultures of fused cells secrecting antibody of predined specificity," *Nature* 256:495-497 (1975);
- Kennet, R.H., "*Monoclonal Antibodies, Hybridoma--A New Dimension in Biological Analysis*," Plenum Press, NY (1980);
- Kozbor and Roder, "The production of monoclonal antibodies from human lymphocytes," *Immunol. Today* 4:72-79 (1983);
- Elzaim, *et al.*,"Generation of Neutralizing Antipeptide Antibodies to the Enzymatic Domain of *Pseudomonas aeruginosa* Exotoxin A," *Infect. Immun.* May;66(5):2170-9 (1998);
- Kettleborough, *et al.*,"Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation," *Protein Engineering* 4(7):773-783 (1991);
- Rothermel *et al.*, "Nucleotide and corrected amino acid sequence of the functional recombinant rat anaphylatoxin C5a," *Biochim. Biophys. Acta* 1351:9-12, (1997);
- Babkina, I.N., *et al.*, *Bioorg Khim*, May;21(5):359-64, (1995)[1];
- Gerard, C. *et al.*, "Amino Acid Sequence of the Anaphylatoxin from the fifth Component of Porcine Complement," *J. Biol. Chem.* 255(10), 4710-4715, (1980);
- Zarbock, J., *et al.*,"A proton nuclear magnetic resonance study of the conformation of bovine anaphylatoxin C5a in solution," *FEBS Lett.* 238(2), 289-294 (1988);
- Stryer ed., *Biochemistry*, 2nd ed,, WH Freeman and Co.(1981);
- Nilsson, *et. al.*, "Affinity Fusion Strategies for Detection, Purification, and Immobilization of Recombinant Proteins," *Protein Expression and Purification.* 11:1-16 (1997);
- Gluzman, "SV40-Transformed Simian Cells Support the Replication of early SV40 Mutants," *Cell*, 23:175-182 (1981);
- Davis *et al.*, *Basic Methods in Molecular Biology*, (1986);

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[1] We have been unable to locate this reference, if the examiner request a copy we will seek to obtain it.

- Wilson, *et al.*,"The Structure of an Antigenic Determinant in a Protein," *Cell* 37:767-778 (1984);
- Evans *et al.*, "An engineered poliovirus chimaera elicits broadly reactive HIV-1 neutralizing antibodies," *Nature* 339:385-388 (1989);
- Huang *et al.*,"Vaccinia Virus Recombinants Expressing an 11-Kilodalton β-Galactosidase Fusion Protein Incorporate Active β-Galactosidase in Virus Particles," *J. Virol.* 62:3855-3861 (1988);
- Schlienger *et al.*,"Human Immunodeficiency Virus Type 1 Major Neutralizing Determinant Exposed on Hepatitis B Surface Antigen Particles is Highly Immunogenic in Primates," *J. Virol.* 66:2570-2576 (1992);
- Posnett *et al.*,"A Novel Method for Producing Anti-peptide Antibodies," *JBC* 263:1719-1725 (1988);
- Nardelli *et al.*,"A Chemically Defined Synthetic Vaccine Model for HIV-1," *J. Immunol.* 148:914-920 (1992);
- *Current Protocols in Molecular Biology*, Eds. Ausabel *et al.*, N.Y.: John Wiley & Sons, (1991)[2];
- Hochuli *et al.*, "New Metal Chelate Adsorbent Selective for Proteins and Peptides Containing Neighbouring Histidine Residues," *J. Chromatography* 411:177-184 (1987);
- Caruthers *et al.*, "New chemical methods for synthesizing polynucleotides," *Nuc. Acids Res. Symp. Ser.* 7:215-233 (1980);
- Crea and Horn, "Synthesis of oligonucleotides on cellulose bya phosphotriester method," *Nuc. Acids Res.* 9:2331 (1980);
- Matteucci and Caruthers,"The Synthesis of Oligodeoxypyrimidines on a Polymer Support," *Tetrahedron Lett* 21:719-722 (1980);
- Chow and Kempe, "Synthesis of oligodeoxyribonucleotides on silica gel support," *Nuc. Acids Res.* 9:2807-2817 (1981);
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[2] This reference is not included. This is a text book which is meant for the general knowledge without any specific pages mentioned.

- Roberge *et al.*,"A Strategy for a Convergent Synthesis of *N*-Linked Glycopeptides on a Solid Support," *Science* 269:202-204 (1995);
- R.C. Bone, "The Pathogenesis of Sepsis," *Ann. Intern. Med.* 115:457-469 (1991);
- E.S. Caplan and N. Hoyt, "Infection Surveillance and Control in the Severely Traumatized Patient," *Am. J. Med.* 70:638-640 (1981);
- M. Meek *et al.*,'The Baltimore Sepsis Scale: Measurement of Sepsis in Patients with Burns Using a New Scoring System," *J. Burn Care Rehab.* 12:564-568 (1991);
- R.L. Nichols in Decision Making in Surgical Sepsis, B.C. Decker, Inc., Philadelphia, "Classification of Surgical Wounds and Nonoperative Factors Influencing Surgical Wound Infection," pp. 20-21 (1991);
- Stahel, *et al.*,"TNF-α-Mediated Expression of the Receptor for Anaphylatoxin C5a on Neurons in Experimental Listeria Meninggoencephalitis," *J. Immunol.* 159(2):861-9 (1997);
- W.K. Joklik *et al.* (eds.), Zinsser Microbiology, 18th ed., Chapter 27 *Streptococcus pneumoniae*, p. 485-489, Appleton-Century-Crofts, Norwalk, CT (1984);
- J.M. Slack and I.S. Snyder, *Bacteria and Human Disease,* pp. 128-133, Yearbook Medical Publishers (1978);
- G.P. Youmans *et al.*, Biologic and Clinical Basis of Infectious Diseases, 3d ed., "Central Nervous System Infection: General Consideration," pp. 552-568, W.B. Saunders Co., (1985);
- Hill, J.H. and Ward, P.A.,"The Philogistic Role of C3 Leukotactic Fragments in Myocardial Infarts of Rats," *J. Exp. Med.* 133:885-900 (1971);
- Mulligan, M.S. *et al.*,"Requirement and Role of C5a in Acute Lung Inflammatory Injury in Rats," *J. Clin. Invest.* 98:503-512 (1996) and
- Deitch, E.A. *Schock* 9:1-11, (1997)[3];

[3] We have been unable to locate this reference, if the examiner request a copy we will seek to obtain it.

Applicants have become aware of the following printed publications which may be material to the examination of this application:

- Mohr M. *et al.*, "Effects of anti-C5a monoclonal antibodies on oxygen use in a porcine model of severe sepsis," *Eur J Clin Invest* 28:227-234 (1998) describe the use of a monoclonal antibody directed to the C terminal of porcine C5a (C5a18C) in a porcine model of sepsis. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- Stevens JH. *et al.*, "Effects of Anti-C5a Antibodies on the Adult Respiratory Distress Syndrome in Septic Primates," *J Clin Invest* 77:1812-1816 (1986) describe the attenuation of respiratory and hemodynamic effects of acute *E. coli* induced sepsis by the administration of rabbit polyclonal anti-C5a des arg antibodies to *Macaca fascicularis* primates. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- Park KW. *et al.*, "Attenuation of Endothelium-Dependent Dilation of Pig Pulmonary Arterioles After Cardiopulmonary Bypass Is Prevented by Monoclonal Antibody to Complement C5a," *Anesth Analg* 89:42-48 (1999) investigates the potential role of C5a in pulmonary endothelial dysfunction associated with cardiopulmonary bypass in pigs by treatment with antibodies raised against purified porcine C5a.. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.

The following references were cited in an International Search Report in the parent case:

- Czermak BJ. *et al.*, "Protective effects of a C5a blockade in sepsis," *Nature Medicine* 5:788-792 (1999) describe the effects of a rabbit polyclonal C5a IgG, raised against the N-terminal region of rat C5a (amino acids 17-36), on sepsis induced by cecal ligation and puncture in rats. The reference does not disclose

a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.

- Kola *et al.*, "Epitope mapping of a C5a neutralizing mAb using a combined approach of phage display, synthetic peptides and site-directed mutagenesis". *Immunotechnology* 1:115-126 (1996) define the epitope of an anti-hC5a specific mAb that recognizes both hC5a and hC5adesArg. The antibody was raised against the C-terminal nonapeptide ISHKDMQLG (C5a-(65-73). The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- Ames RS *et al.*, "Isolation of Neutralizing Anti-C5a Monoclonal Antibodies from a Filamentous Phage Monovalent Fab Display Library," *J Immunol* 152:4572-4581 (1994) describe the isolation of monoclonal Fabs from a phage display library. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- PCT Application WO 96/39503 describes C5a analogues or polypeptide derivatives that are C5a antagonists but do not have C5a agonist activity. Some of the derivatives result from modifications of the C terminal region of C5a. The disclosure also discusses antibodies specific for the C5a analogues and derivatives, wherein the antibodies exhibit substantially no cross-reactivity to human C5a. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- EP 0 245 993 A2 describes monoclonal antibodies against human C5a and human des-arg74-C5a. The monoclonal antibodies are said to bind specifically to human C5a or its des-arg derivative to block adverse effects of C5a and its des-arg derivative. In particular, the antibodies may be part of a composition useful for treatment of subjects who suffer from a condition associated with injurious intravascular complement activation, such conditions including Gram-

negative sepsis. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.

The following references were cited by the examiner in the parent case:

- Protein Accession Number A57689/ GI "2118416" provides the 77 amino acid sequence of rat complement C5a. There is no discussion of a method of administering anti-C5a antibodies to a patient with symptoms of sepsis.
- Protein Accession Number P01032/ GI "116605" provides a summary of the biological function and the 74 amino acid sequence of complement C5a anaphylatoxin from the pig. There is no discussion of a method of administering anti-C5a antibodies to a patient with symptoms of sepsis.
- Protein Accession Number P12082/ GI "116604" provides a summary of the biological function and the 74 amino acid sequence of bovine complement C5a anaphylatoxin. There is no discussion of a method of administering anti-C5a peptide region antibodies to a patient with symptoms of sepsis.
- U.S. Patent 5,340,923 to Carroll describes the preparation and purification of antivenoms effective against a variety of venoms. The antivenoms are raised in chickens, and commercial horse antivenoms are subject to the purification procedures. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- Zhong G. *et al.*, "Production, specificity, and functionality of monoclonal antibodies to specific peptide-major histocompatibility complex class II complexes formed by processing of exogenous protein" *Proc Natl Acad Sci USA* 94:13856-13861 (1997) describe production of monoclonal antibodies which recognize hen egg lysozyme peptide fragments complexed with MHC II receptors. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.

- Larrick JW *et al.*, "Characterization of Murine Monoclonal Antibodies That Recognize Neutralizing Epitopes on Human C5a" *Infection and Immunity* 55:1867-1872 (1987), describe the production of murine monoclonal antibodies specific for human C5a. The antibodies were raised against purified C5a, and bind both C5a and des-Arg C5a. In the discussion section, the authors note that "Although we have not directly tested the MAbs in a model of sepsis, it is reasonable to expect that they would give protection in human patients because they neutralize passively administered human C5a in rabbits." The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.
- Hatherhill JR *et al.*, "Effects of Anti-C5a Antibodies on Human Polymorphonuclear Leukocyte Function: Chemotaxis, Chemiluminescence, and Lysosomal Enzyme Release" *J of Biological Response Modifiers* 8:614-624 (1989), describe experiments designed to address the action of monoclonal and polyclonal anti-C5a antibodies on in vitro PMN functions. The polyclonal antibodies were raised in rabbits against human C5a des-Arg, while the monoclonal antibody was raised in mice against porcine C5a. The reference does not disclose a method of treating a human with sepsis comprising the administration of a therapeutic composition comprising an antibody specific for SEQ ID NO.: 2 to said human.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: March 24, 2003

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